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A straightforward, highly stereoselective construction of eight stereogenic centers in (+)-discodermolide C_1–C_{13} segment, based on a strategy of iterative aldol reactions

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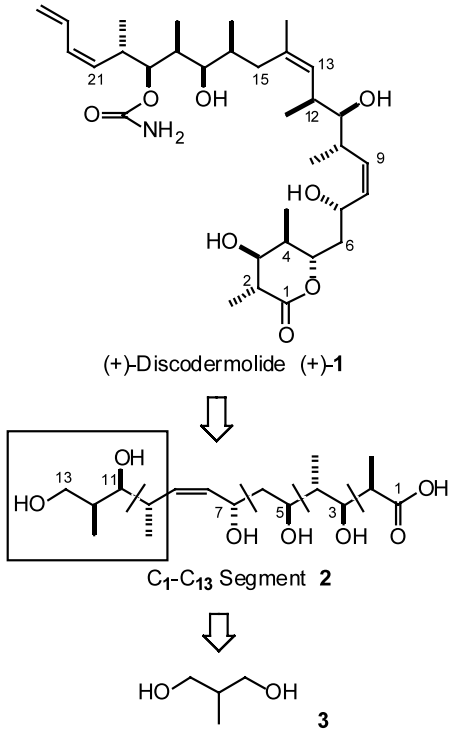
Abstract—The eight stereogenic centers were introduced into the C_1–C_{13} segment of (+)-discodermolide by iterative aldol reactions with quite a high level of selection.

(+)-Discodermolide, (+)-**1**, is a polypropionate-derived natural product known as a potent microtubule-stabilizing agent,[1] and synthetical supply is necessary for utilizing its remarkable characteristics of immunosuppression[1a] and cytotoxicity.[1b] In addition, its unique polyketide structure bearing 13 stereogenic centers is an attractive pure target for synthetic chemists. Since the absolute configuration of discodermolide was determined by Schreiber,[2a,b] numerous synthetic studies are continuing to date.[2,3] However, there have been few approaches based on Lewis acid-mediated aldol reactions, because no reliable methodology has been established for diastereoselectively constructing *syn*- and *anti*-propionates in sequence. Our synthetic target is the C_1–C_{13} segment, **2**, of (+)-**1**, having eight stereogenic centers, as shown in Scheme 1, where the four slant lines present the suitable positions for the planned bond formations with sequential four aldol reactions. We disclose herein a unique approach introducing all the stereocenters of **2** *by iterative Lewis acid-mediated aldol reactions with high stereoselection.*

The elaboration to the target **2** was started with the chiral oxazaborolidinone (**L-5**)-promoted asymmetric aldol reaction of racemic aldehyde **4**, derived from achiral diol **3**, with tetra-substituted silylketene acetal **6**. The selectivity behavior in the asymmetric transformation from racemic aldehyde **4** to enantiopure stereotriad **8** has been described *in detail* in the preceding paper[4] in connection with dissymmetrization of the starting diol **3**. *The first chiral borane-promoted aldol reaction* quite effectively resulted in the introduction of the stereo-



Scheme 1.

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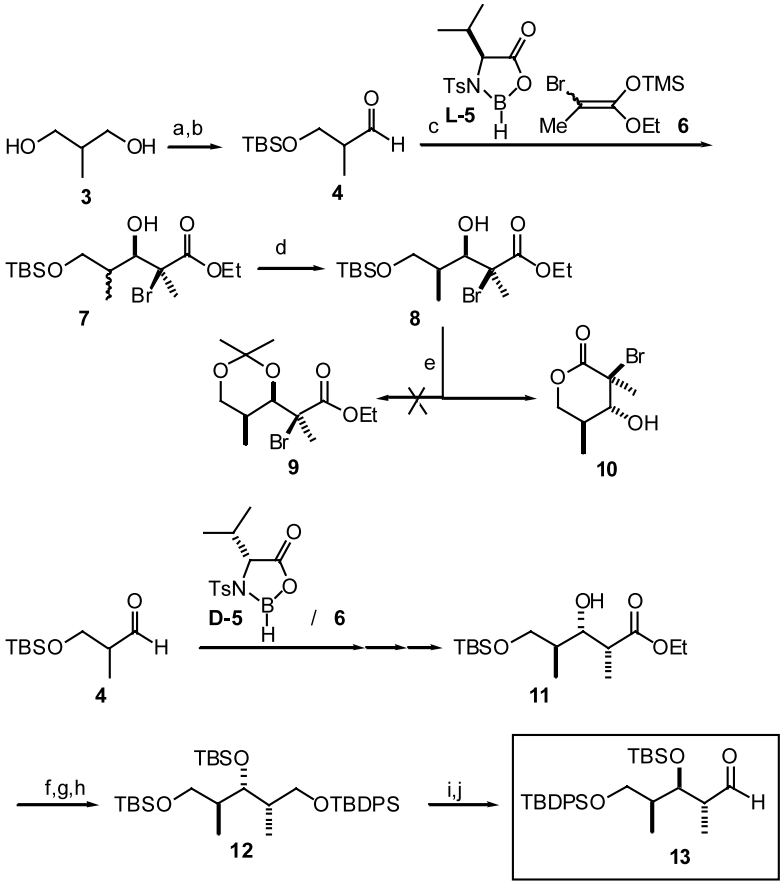
genic centers at C-11 and C-12 into **2**. Conversion of **8** to cyclic compound **9** was required, because **9** is prone to allow high 2,3-*anti* diastereoselection through the so-called 'exocyclic effect'[5] in the debromination process. However, acidic deprotection of 3,4-*syn* **8** unfortunately underwent cyclization to the corresponding δ-valerolactone **10**.[3a,6] We therefore selected an alternative route to 2,3-*anti*-3,4-*syn* stereotriad **13** by conversion from 2,3-*syn*-3,4-*anti* **11**, which has the opposite stereochemistry relative to **13**. The preparation of **11** has been reported using **D-5** in the preceding paper.[4] The switching of the stereochemistry of **11** to the opposite one, which corresponds to that of **13**, would be realized by replacing the functional groups at both terminals of **11**. Actually, the desired stereotriad **13** was obtained after the following five-step reaction sequence: TBS protection, DIBALH reduction to the corresponding alcohol, TBDPS protection, selective deprotection, and Swern oxidation, in good overall yield (Scheme 2). Thus, the three stereogenic centers in **2** could be eventu-



Scheme 2. *Synthesis of intermediate aldehyde **13**:* (a) TBSCl, NaH, THF, rt, 15 h, 91%; (b) Swern: $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, Et_3N, 0°C, 90%; (c) L-TsValine, BH_3·THF, **6**, −78°C, 10 h, 80%; (d) silica gel column chromatography; (e) PTSA, MeOH, rt, 1 h, 95%; (f) TBSOTf, 2,6-lutidine, rt, 1 h, 87%; (g) DIBALH, CH_2Cl_2, −78°C, 3 h, 80%; (h) TBDPSCl, imidazole, CH_2Cl_2, rt, 1 h, 92%; (i) PTSA, MeOH, rt, 20 h, 90%; (j) Swern, 87%.

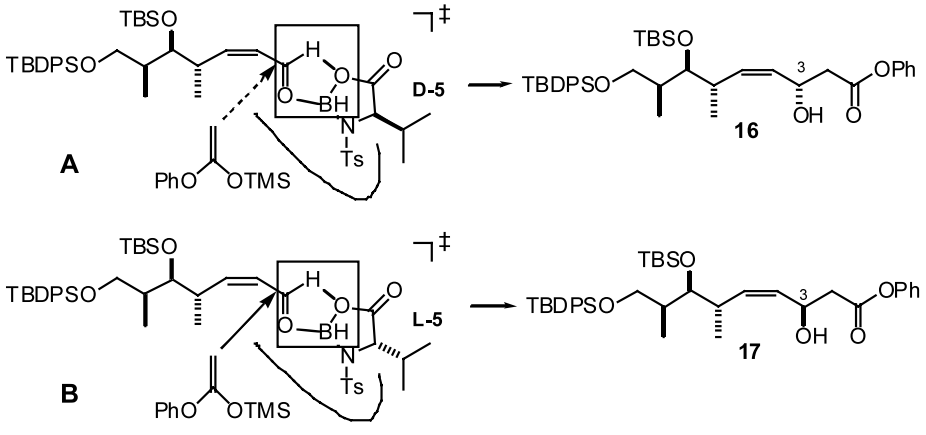
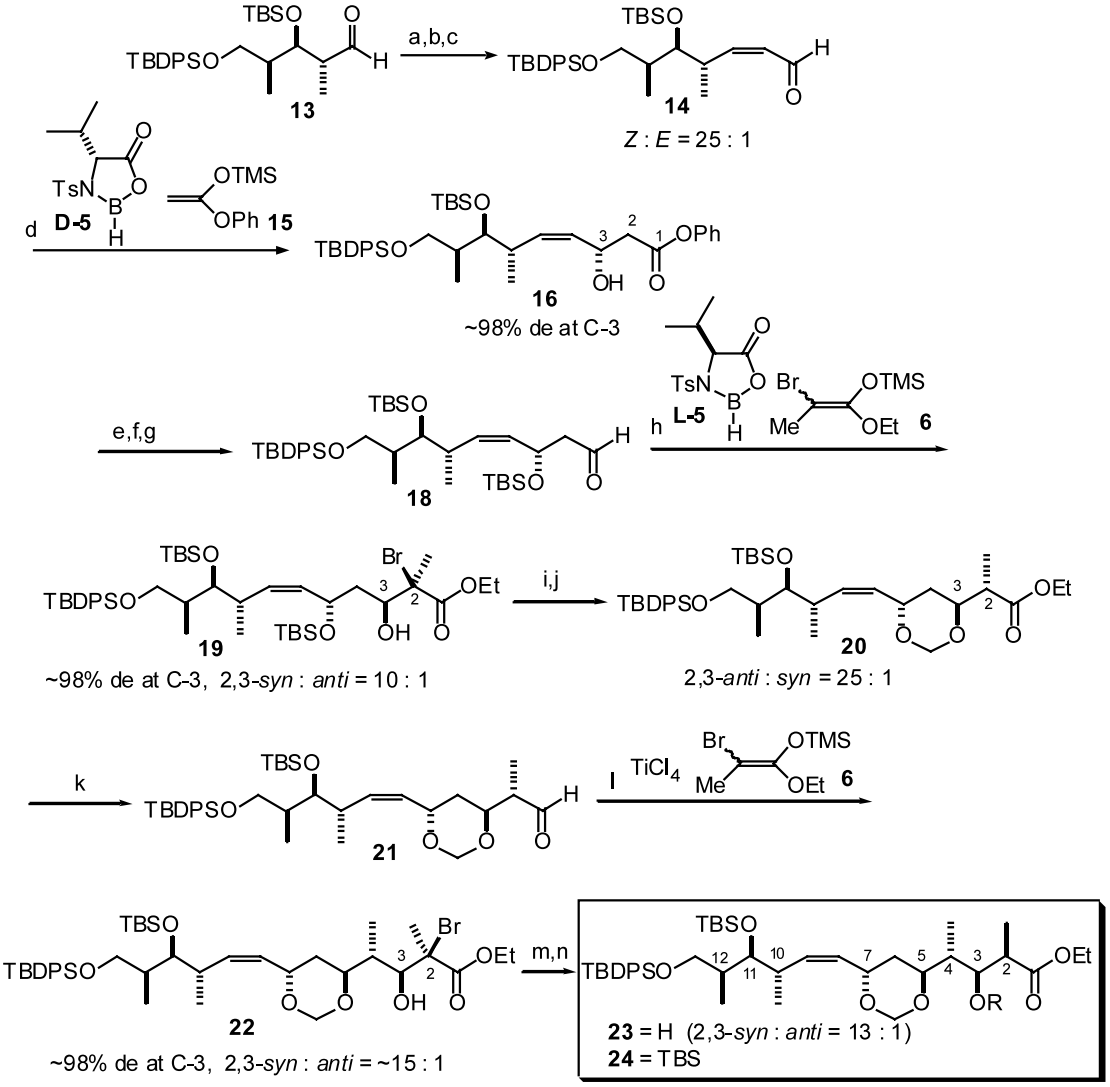


Figure 1. Catalyst (promoter) control on facial selection.

ally introduced by the first aldol reaction coupled with the following radical debromination reaction.

The aldehyde **13** was converted into the corresponding *Z*-enoate in 95% yield (*Z*:*E*=25:1), according to the Still procedure of the Horner–Wadsworth–Emmons reaction.[7] After DIBALH reduction of the *Z*-enoate, followed by Swern oxidation to the *Z*-enal **14**, **14** was subjected to *the second aldol reaction* using a silyl nucleophile **15**, related to an acetate equivalent, in order to create the next chiral center. At this stage, the chiral oxazaborolidinoine-promoted asymmetric aldol reaction played an extraordinary role in creating the desired stereocenter in the carbon–carbon bond formation. When we used **D-5**, the expected **16** was obtained with almost complete selection, while **L-5** led to the epimer **17** with the same level of selection. The configuration created at C-3 in these aldol adducts surely came from the stereocenter of the used promoters in a superior manner of catalyst (promoter) control on facial selection (Fig. 1).[8] The following sequence of TBS protection, DIBALH reduction, and Swern oxidation provided the aldehyde **18** in good overall yield. *The third aldol reaction* of **18** with the chiral borane **L-5** furnished α-bromo ester **19** in 89% yield with almost complete selection at C-3 with the isomers at C-2 (2,3-*syn*:*anti*=10:1). Protection of the hydroxy group at C-3 of **19** with dimethoxymethane in the presence of P_2O_5 eventually gave a cyclic acetal in good yield, accompanied with deprotection of the neighboring TBS group. The usual radical debromination resulted in good *anti* selection (2,3-*anti*:*syn*=25:1) to give **20**, presumably with the exocyclic effect mentioned above. Thus, the remarkable efficiency of our strategy, comprised of the asymmetric aldol reaction coupled with radical debromination, was ascertained again in establishing the additional two stereocenters. *The last aldol reaction* using a sequence of the Mukaiyama aldol



Scheme 3. *Reagents and conditions:* (a) $(CF_3CH_2O)_2P(O)CH_2COOCH_3$, 18-crown-6, KHMDS, THF, −78°C, 15 h, 95%; (b) DIBALH, CH_2Cl_2, −78°C, 3 h, 90%; (c) Swern, 86%; (d) D-TsValine, BH_3·THF, **15**, −78°C, 16 h, 86%; (e) TBSOTf, 2,6-lutidine, rt, 1 h, 87%; (f) DIBALH, CH_2Cl_2, −78°C, 3 h, 80%; (g) Swern, 90%; (h) L-TsValine, BH_3·THF, **6**, −78°C, 89%; (i) $CH_2(OCH_3)_2$, $CHCl_3$, P_2O_5, rt, 1 h, 80%; (j) Bu_3SnH, Et_3B, toluene, −78°C, 3 h, 85%; (k) DIBALH, CH_2Cl_2, −78°C, 3 h, 90%; (l) $TiCl_4$, **6**, −78°C, 30 min, 78%; (m) Bu_3SnH, Et_3B, $MgBr_2$·OEt_2, −78°C, 15 h, 80%; (n) TBSOTf, 2,6-lutidine, 97%.

reaction was designed to proceed through a chelation pathway, and the following radical reduction could be predicted to be difficult to achieve the expected 2,3-*syn*-3,4-*anti* selection.[9] However, contrary to the prediction, $TiCl_4$-mediated aldol reaction of **21** with **6** was dramatically realized to produce the 3,4-anti product **22** with excellent anti selection (~98% de) along with the minor isomers at C-2 (2,3-*syn*:*anti*= ~15:1). After the usual debromination with Bu_3SnH/Et_3B in the presence of $MgBr_2{\cdot}OEt_2$, the last stereogenic center at C-2 was achieved (2,3-*syn*:*anti*=13:1), followed by TBS protection to give the target equivalent **24** of **2** (Scheme 3).[10]

In conclusion, the eight stereogenic centers in C_1–C_{13} segment **2** of (+)-discodermolide were introduced by four aldol reactions with quite a high level of selection. The strategy, based on the iterative aldol reactions, turned out to be practically effective for the straightforward synthesis of polypropionate frameworks.

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8. In the boron-mediated aldol reactions of similar γ-chiral (*Z*)-enals, competition between reagent control and substrate control has been observed (Ref. 3j).
9. Even $TiCl_4$ did not serve the expected chelation control in the reaction of aldehydes having a substituent at the β-position. See: Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322.
10. Spectroscopic data for selected compounds.
Compd **13**: $[\alpha]_D^{27}$ −15.0 (*c* 2.0, $CHCl_3$). IR (neat) 2959, 2932, 2887, 2858, 1726 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.03 (s, 3H), 0.05 (s, 3H), 0.85 (s, 9H), 0.86 (d, *J*=6.8 Hz, 3H), 1.03 (d, *J*=6.8 Hz, 3H), 1.08 (s, 9H), 1.76–1.86 (m, 1H), 2.54–2.62 (m, 1H), 3.50 (dd, *J*=10.3, 6.1 Hz, 1H), 3.58 (dd, *J*=10.2, 7.6 Hz, 1H), 4.16 (dd, *J*=6.1, 3.2 Hz, 1H), 7.36–7.46 (m, 6H), 7.65 (dt, *J*=7.6, 1.4 Hz, 4H), 9.75 (d, *J*=2.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) −4.2. −4.1, 11.1, 11.6, 18.3, 19.2, 26.0, 26.9, 39.7, 50.9, 65.9, 73.4, 127.6, 127.7, 129.6, 129.7, 133.7, 135.5, 135.6, 204.9.
Compd **16**: $[\alpha]_D^{26}$ +19.6 (*c* 1.43, $CHCl_3$). IR (neat) 3454, 2959, 2930, 2858, 1759, 1595 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.02 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 0.88 (d, *J*=6.8 Hz, 3H), 0.94 (d, *J*=6.8 Hz, 3H), 1.07 (s, 9H), 1.83 (dq, *J*=6.8, 3.2 Hz, 1H), 2.40 (d, *J*=3.4, 1H), 2.69 (dd, *J*=15.6, 4.9 Hz, 1H), 2.67–2.75 (m, 1H), 2.80 (dd, *J*=15.8, 8.0 Hz, 1H), 3.46 (dd, *J*=10.0, 6.6 Hz, 1H), 3.59 (dd, *J*=10.0, 6.8 Hz, 1H), 3.73 (dd, *J*=5.4, 3.2 Hz, 1H), 4.82–4.88 (m, 1H), 5.47 (dd, *J*=10.9, 7.6 Hz, 1H), 5.54 (t, *J*=10.7 Hz, 1H), 7.09–7.66 (m, 15H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) −4.1, −3.2, 11.8, 18.5, 19.1, 19.2, 26.2, 26.9, 36.9, 40.0, 42.2, 64.4, 66.5, 75.7, 121.6, 125.9, 127.6, 129.4, 129.5, 129.6, 130.0, 133.9, 135.6, 136.8, 150.5, 170.2.
Compd **20**: $[\alpha]_D^{28}$ −4.9 (*c* 1.03, $CHCl_3$). IR (neat) 2959, 2932, 2858, 1738 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) −0.01 (s, 3H), 0.05 (s, 3H), 0.06 (s, 3H), 0.86 (d, *J*=6.8 Hz, 3H), 0.87 (s, 9H), 0.92 (d, *J*=7.1 Hz, 3H), 1.05 (s, 9H), 1.10 (d, *J*=7.1 Hz, 3H), 1.27 (t, *J*=7.1 Hz, 3H), 1.52–1.61 (m, 1H), 1.77–1.90 (m, 2H), 2.61–2.67 (m,

1H), 2.71 (dq, $J=8.8$, 7.1 Hz, 1H), 3.43 (dd, $J=9.8$, 6.8 Hz, 1H), 3.56 (dd, $J=10.0$, 6.4 Hz, 1H), 3.74 (t, $J=3.7$ Hz, 1H), 3.99 (dt, $J=9.3$, 3.2 Hz, 1H), 4.17 (d, $J=7.1$ Hz, 2H), 4.63–4.67 (m, 1H), 4.72 (d, $J=6.6$ Hz, 1H), 4.82 (d, $J=6.6$ Hz, 1H), 5.62–5.69 (m, 2H), 7.35–7.45 (m, 6H), 7.63–7.67 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) –4.1, –3.7, 12.2, 12.8, 14.2, 18.4, 18.7, 19.3, 26.1, 26.9, 31.6, 37.0, 40.1, 43.9, 60.5, 66.6, 67.7, 73.5, 75.5, 88.0, 126.2, 127.6, 129.5, 129.6, 133.9, 134.0, 135.6, 137.8, 174.4.

Compd **24**: $[\alpha]_D^{28}$ –20.5 (c 0.44, $CHCl_3$). IR (neat) 2959, 2932, 2856, 1734 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) –0.02 (s, 3H), 0.04 (s, 6H), 0.07 (s, 3H), 0.85 (d, $J=6.8$ Hz, 3H), 0.86 (s, 9H), 0.87 (d, $J=6.8$ Hz, 3H), 0.89 (s, 9H), 0.91 (d, $J=6.8$ Hz, 3H), 1.05 (s, 9H), 1.14 (d, $J=7.1$ Hz, 3H), 1.24 (t, $J=7.1$ Hz, 3H), 1.49 (dt, $J=13.7$, 2.7 Hz, 1H), 1.76–1.98 (m, 3H), 2.60–2.67 (m, 2H), 3.43 (dd, $J=10.0$, 6.8 Hz, 1H), 3.54 (dd, $J=10.0$, 6.6 Hz, 1H), 3.67 (dt, $J=10.9$, 2.9 Hz, 1H), 3.73 (t, $J=3.9$ Hz, 1H), 4.09 (q, $J=7.1$ Hz, 2H), 4.24 (dd, $J=5.6$, 4.4 Hz, 1H), 4.65–4.73 (m, 1H), 4.70 (d, $J=6.3$ Hz, 1H), 4.83 (d, $J=6.6$ Hz, 1H), 5.61 (t, $J=10.2$ Hz, 1H), 5.71 (dd, $J=11.2$, 7.8 Hz, 1H), 7.35–7.44 (m, 6H), 7.61–7.68 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) –4.4, –4.3, –4.1, –3.7, 10.5, 12.0, 13.6, 14.1, 18.2, 18.4, 18.5, 19.3, 25.9, 26.1, 26.9, 33.8, 37.1, 40.0, 42.0, 43.4, 60.3, 66.7, 67.9, 72.1, 72.6, 75.3, 87.9, 126.4, 127.6, 129.4, 129.5, 133.9, 134.0, 135.6, 137.3, 175.8.